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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,216	01/20/2004	Stephen F. Kingsmore	071949-5914	6434

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
08/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,216	KINGSMORE ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-23 and 96-108* is/are pending in the application.

4a) Of the above claim(s) *5,6,9-18,20-23 and 96-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8, 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/16/2006, 7/25/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed 10/16/2006 are acknowledged. It is noted that the examiner of record has changed. Future correspondence should be addressed to Brian Gangle, Art Unit 1645.

Election/Restrictions

Applicant's election of Group I in the reply filed on 10/16/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon consideration of the amendment, a further restriction, as set forth below, is applied to the elected claims.

Biomarker Election Requirement Applicable to All Claims

The pending claims read on patentably distinct methods of diagnosing sepsis in a human subject. is patentably distinct because they are molecules with differing biochemical and immunological properties and a further restriction is applied to the claims.

Each combination of biomarkers is independent or distinct because as disclosed the different biomarkers have mutually exclusive characteristics because they are molecules with differing biochemical and immunological properties. In addition, these combinations of biomarkers are not obvious variants of each other based on the current record and a further restriction is applied to the claims.

There is an examination and search burden for these patentably distinct combinations due to their mutually exclusive characteristics. Each of the biomarkers requires a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. In addition, art that applies to claim 1 would not be sufficient to reject the dependent claims with additional biomarkers.

Applicant must further elect a single combination of biomarkers.

Applicant is advised that examination will be restricted to only the elected combination of biomarkers and this should not be construed as a species election.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Barry Wilson on 7/26/2007, a provisional election was made with traverse to prosecute the combination of MPIF-1 and TNF-R1. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 1-6, 8-23, and 96-108 are pending. Claims 5-6, 9-18, 20-23, and 96-108 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-4, 8, and 19 are currently under examination.

Information Disclosure Statement

The information disclosure statements filed on 11/16/2006 and 7/25/2007 are acknowledged. Initialed copies are enclosed.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: 5A-5E and 6A-6E. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 9. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1-4 and 19 are objected to because of the following informalities: the claims are drawn, in part, to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of

knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of diagnosing sepsis in a human subject, comprising determining the concentration of myeloid progenitor inhibitory factor-1 (MPIF-1) and tumor necrosis factor receptor-1 (TNF-R1) in a sample and comparing said concentration to corresponding reference concentrations, selected to indicate the presence or absence of sepsis, wherein said reference concentration is determined using one or more control samples obtained from one or more human subjects not suffering from sepsis. For claims 1-4 and 8, an elevated concentration of MPIF-1 in the test sample, relative to the reference concentration, is indicative of the presence of sepsis; and for claim 19, an elevated concentration of both MPIF-1 and TNF-R1 is indicative of sepsis.

Breadth of the claims: The claims encompass the detection of sepsis, which is defined in the specification as an infection-induced syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation. It is noted that this definition encompasses many conditions and diseases that are not considered sepsis by the art. This includes diseases such as influenza, roseola, as well as conditions associated with trauma and surgery. The method further encompasses samples of all types from humans, including hair and tissue samples other than blood or serum.

Guidance of the specification/The existence of working examples: The specification discloses information about sepsis, which is defined in the specification as an infection-induced

syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation. The specification teaches that there are multiple biomarkers that have been associated with sepsis, mostly these are cytokines associated with inflammation. Of these cytokines, some information is given on myeloid progenitor inhibitory factor-1 (MPIF-1) and tumor necrosis factor receptor-1 (TNF-R1). MPIF-1 is a cytokine that binds to CCR1. The specification states that there is no literature describing a direct association between MPIF-1 levels and sepsis, which concurs with the examiner's findings. Of TNF-R1, the specification states, "soluble TNF receptor levels were elevated in trauma patients compared to healthy persons. Severe trauma led to enhanced sTNF-R1 levels on scene and on hospital admission." Increased TNF-R1 levels are also associated with sepsis. The specification provides several studies where the levels of various biomarkers were determined in patients with sepsis and compared to those in patients without sepsis. Statistical evaluations of these data are presented which show conflicting results. Three studies were undertaken to identify suitable biomarkers for the diagnosis of sepsis. For MPIF-1, study 1 showed a significant difference between healthy and septic individuals in both serum and plasma samples. However, study 2 showed the increase only in plasma and not in serum. Also, TNF-R1 was not identified in either study as a potential marker. In study 3, MPIF-R1 was increased in septic individuals, as was TNF-R1. The specification addresses the differences in results by listing the differences between the studies. Studies 1 and 2 were small, involving 6 and 12 patients, respectively; whereas study 3 involved 240 sepsis patients. In study 3, the patients had more severe sepsis than those in studies 1 and 2. In addition, the comparisons in studies 1 and 2 were between healthy patients and septic patients, while in study 3, the comparison was between ill, but non-septic patients and septic patients. Finally, studies 1 and 2 involved plasma and serum samples, while study 3 involved diluted serum.

State of the art: As stated above, there is nothing in the prior art that directly links MPIF-1 levels with sepsis, although it is linked with inflammation. TNF-R1 is linked with sepsis, but also with other conditions. Kimura *et al.* (British J. Surg., 85:1631-1635, 1998) showed that TNF-R1 is produced in response to surgical stress, and may be further enhanced by intraoperative bacterial translocation. They suggest that plasma TNF-R1 concentrations may be

predictive of postoperative infectious complications (including peritoneal abscess and pneumonia, which are not necessarily conditions of sepsis) (see Table 1 and page 1634, final paragraph). Dollner *et al.* (Biol. Neonate, 80:41-47, 2001) showed that both neonates suffering from various non-infected conditions (such as respiratory distress, intraventricular haemorrhage, and icterus neonatorum) as well as neonates with infection, had higher TNF-R1 (also known as p55) levels than healthy controls (see Table 3). Doellner *et al.* (Early Human Dev., 52:251-261, 1998) attempted to use serum concentrations of TNF-R1 as a diagnostic indicator of sepsis in neonates. However, they found that the specificity of TNF-R1 concentrations was low. They stated, "our data do not suggest that assessment of sTNFR may improve the accuracy of diagnosing early onset neonatal sepsis compared to using CRP. The usefulness of sTNFR as diagnostic tests for infection later in the neonatal period remains to be elucidated" (page 259, final paragraph). Slotwinski *et al.* (J. Clin. Immunol., 22:289-296, 2002) used TNF-R1 to predict local infective complications after colorectal surgery. Slotwinski *et al.* found that TNF-R1 was significantly elevated immediately after liver resection, as well as in patients with post-operative complications (page 295, paragraph 1).

It is clear from the art and the specification that both MPIF-1 and TNF-R1 are involved in the inflammatory process. However, both of these cytokines are known to be involved, not just in systemic inflammation, but in local inflammation. The specification does not provide guidance showing the levels of either cytokine that are necessary to for a diagnosis of sepsis, and no means has been provided to differentiate between the increase in cytokines associated with trauma, burns, or other infections and the increase associated with sepsis. In fact, the specification shows that, in two studies, TNF-R1 was not found to be associated with sepsis, while MPIF-1 had a different association with sepsis, depending on the sample source. It is suggested in the specification that TNF-R1 was not identified in studies 1 or 2 because these studies were smaller and because, in study 3, the patients had more severe sepsis than those in studies 1 and 2. However, the fact that severe sepsis was required for TNF-R1 levels to be significantly raised further highlights the fact that increased TNF-R1 levels are unacceptable for the diagnosis of sepsis.

Moreover, applicant's definition of sepsis as an infection-induced syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia,

leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation is very broad. Numerous diseases that would not be considered related to sepsis by those in the art are encompassed by this definition, and there is no evidence whatsoever to link MPIF-1 or TNF-R1 levels with these diseases. For example, both influenza and roseola are viral infections that cause fever and leukopenia. A child with the flu would meet the instant definition of being septic, but would not be considered as such by those in the art, and there is no research that suggests one could use increased levels of MPIF-1 and TNF-R1 to diagnose said child as septic. Finally, all samples from humans are encompassed by claims 1, 8, and 19. As MPIF-1 and TNF-R1 are involved in inflammatory processes, they would be present in samples from local infections, but this would not be indicative of systemic inflammation.

Consequently, in view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use the invention as claimed; therefore the claims are not enabled.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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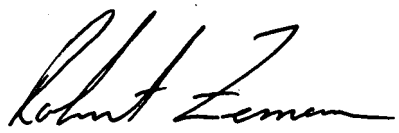
Brian Gangle
AU 1645



ROBERT A. ZEMAN
PRIMARY EXAMINER